

Combining generative artificial intelligence and on-chip synthesis for de novo drug design

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Abstract

Generative deep learning and miniaturized bench-top synthesis were combined to automate the design of novel LXR agonists. Automating the molecular design-make-test-analyze cycle accelerates hit and lead finding for drug discovery. Using deep learning for molecular design and a microfluidics platform for on-chip chemical synthesis, liver X receptor (LXR) agonists were generated from scratch. The computational pipeline was tuned to explore the chemical space of known LXR α agonists and generate novel molecular candidates. To ensure compatibility with automated on-chip synthesis, the chemical space was confined to the virtual products obtainable from 17 one-step reactions. Twenty-five de novo designs were successfully synthesized in flow. In vitro screening of the crude reaction products revealed 17 (68%) hits, with up to 60-fold LXR activation. The batch resynthesis, purification, and retesting of 14 of these compounds confirmed that 12 of them were potent LXR agonists. These results support the suitability of the proposed design-make-test-analyze framework as a blueprint for automated drug design with artificial intelligence and miniaturized bench-top synthesis.